

Serial No.: 08/719,571
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respectively, indicating that the present application contained obvious typographical errors corrected herein.

Applicant respectfully acknowledges the art made of record and not relied upon.

Objection to the Specification Under 35 U.S.C. § 112, First Paragraph

“The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.” Applicant respectfully traverses.

The Office Action addresses specific issues regarding the specification which relate to issues in the claims under 35 U.S.C. § 112, first paragraph. Applicant submits that the issues regarding the specification are resolved below by addressing the issues raised in the rejections of the claims. As such, the Applicant requests withdrawal of the objection to the specification.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-4 and 8-14 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not reasonably provide description or enablement for the claimed invention. Specifically regarding Claims 1-3, the Office Action states, “the specification does not reasonably provide description of or enablement for any and every antibody population specific for a RET protein or for the extracellular domain thereof other than antibodies 3A61D7, 3A61C6 or 2C42H1.” Regarding Claims 8-14, the Office Action states that the specification, “while being enabling for RET+ cell populations from rat, and implicitly mouse, fetal gut, does not reasonably provide enablement or description for any and every neural progenitor cell population from any and every animal species.” Regarding Claims 4 and 12, the Office Action states that “the specification while being enabling for antibodies specific for RET antigen expressed in mice and rats, does not

reasonably provide enablement for any other reagent which specifically binds RET antigen." Applicant respectfully traverses.

A review of the standard to determine enablement

Under 35 U.S.C. § 112, a patent need only contain a written description that enables one skilled in the art to make and use the claimed invention without undue experimentation. Altas Powder Co. V. E.I. Du Pont De Nemours & Co., 224 USPQ 409, 413 (Fed. Cir. 1984). "An inventor need not, however, explain every detail since he is speaking to those skilled in the art." DeGeorge v. Bernier, 226 USPQ 758, 762 (Fed. Cir. 1985). Moreover, "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." In re Gosteli, 10 USPQ 1614, 1618 (Fed. Cir. 1989).

The Court of Appeals for the Federal Circuit (CAFC) has specifically addressed rejections under § 112, first paragraph, in regards to monoclonal antibodies. Specifically, the CAFC has found that the creation of monoclonal antibodies does not require undue experimentation. In re Wands, 8 USPQ2d 1400 at 1406 (CAFC 1988).

Moreover, In re Wands lists factors to consider concerning a § 112, first paragraph rejection. Id. at 1404. The factors are: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Id.

The monoclonal antibodies of Claims 1-3 are described and enabled

Claim 1 has been amended to recite that the antibody is a monoclonal antibody bound to a RET antigen on a cell selected from the group consisting of a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell and a committed

neuronal progenitor (NP) cell. In reviewing the In re Wands factors, the RET monoclonal antibodies of Claims 1-3 are described and enabled.

The Nature of the Invention; The Predictability of the Art and Quantity of Experimentation

Claims 1-3 are drawn to a monoclonal antibody which specifically binds to RET. To a skilled artisan, the generation of monoclonal antibodies is a predictable event with a known antigen. Moreover, as discussed herein, the Court of Appeals for the Federal Circuit has found that the generation of monoclonal antibodies does not require undue experimentation. In re Wands at 1406.

The Guidance in the Specification; Working Example; The Breadth of the Claims

Applicant submits that the specification enables one skilled in the art to make and use a RET antibody as set forth in the claims. In particular, one skilled in the art can use the information published in Hesketh which describes the DNA and amino acid sequence of RET to identify a RET antigen. See page 7, lines 9-16, of the specification beginning with "[t]he sequence of RET is known from several organisms."

Once the antigen has been determined and one skilled in the art has been motivated to generate a monoclonal antibody thereto by the discoveries provided in the specification, i.e., the role of RET as a marker of the fate of cells, the skilled artisan can do so, i.e., by following standard immunization procedures as set forth in specification of the claimed invention. See pages 7-8 of the specification starting on line 19 (page 7) and ending on line 19 (page 8).

Moreover, the specification provides an example of generating monoclonal antibodies to RET. See page 17, line 15 through page 18, line 2 regarding the preparation of the antigen. See page 18, lines 3-13, regarding the production of the antibody. While the Office Action emphasizes that Applicant has only provided one example, Applicant emphasizes that working examples are not always necessary yet

Applicant has provided one none-the-less. This example is meant to be illustrative and to provide guidance, not to limit the claims. Moreover, Claims 1-3 are limited to monoclonal antibodies which specifically bind to the RET antigen. Provided with this guidance, the working example, and the breadth of the claims, the skilled artisan would be able to practice the claimed subject matter.

The Skilled Artisan

The level of skill in the art of generating antibodies is high. Provided with the specification, the skilled artisan could make and use the claimed invention.

Amgen is not applicable to the claimed invention

Applicant points out that In re Wands is applicable to the present case because In re Wands specifically addresses monoclonal antibodies. In contrast, Amgen addresses degenerate DNA sequences. Thus, In re Wands is applicable, and as stated above, the creation of monoclonal antibodies does not require undue experimentation. In re Wands at 1406.

Deposit

Regarding the necessity of a deposit, “[n]o deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.” In re Wands, at 1403. Applicant submits that the specification enables one skilled in the art because the monoclonal antibodies generated from the RET protein can be made from “readily available sources”. Id. at 1404. Monoclonal antibody production can be made without undue experimentation, In re Wands, at 1406, and the RET protein has been described in various publications such that the sequence and domain structure is known (Hesketh). Moreover, pages 17-18 of the specification exemplify to one skilled in the art how to produce the claimed subject matter.

Conclusion

In summary, the specification in combination with the level of skill in the art provides sufficient guidance for one skilled in the art to generate a monoclonal antibody to RET. In particular, not only has this issue been addressed by the Court of Appeals for the Federal Circuit, but the In re Wands factors show that the claimed invention meets the requirements under Section 112, first paragraph. Moreover, Applicant has reasonably conveyed that he invented the claimed subject matter. Therefore, for all the foregoing reasons, Applicant respectfully requests that the rejection be withdrawn.

Neural progenitor cell populations of Claims 8-14 are described and enabled

Applicant points out that one skilled in the art would reasonably expect that using the method as stated in the specification and claims, one could select RET+ neural progenitor cells from various species. Specifically as stated in the specification on page 7, line 9-11, RET is found in several organisms (Hesketh, ed., The Oncogene Facts Book, Academic Press Limited, pp. 241-245 (1995)). Moreover, experiments have demonstrated that many neural crest cells are multipotent in both avian and mammalian embryos (Dupin, E. And Le Douarin, N.M., Proc. Natl. Acad. Sci. USA, 85:5325-5329 (1988); Stemple, D.L. and Anderson, D.J., Cell, 71:973-985 (1992); Ito et al., Dev. Biol., 157:517-525 (1993)). Thus, one skilled in the art would expect to be able to practice the claimed invention using various cell populations. Applicant, therefore, requests that the rejection be withdrawn.

Reagents of Claims 4 and 12 that bind the RET antigen are described and enabled

Applicant submits the skilled artisan can identify reagents which specifically bind to RET. Generally, the skilled artisan would isolate or identify the RET and then would screen for reagents that specifically bind RET using known techniques in the art, e.g. competitive binding assays, sandwich assays, affinity columns. RET is the antigen in the

claimed invention and RET is found in several organisms. (Hesketh, ed., The Oncogene Facts Book. Academic Press Ltd., pp.241-245, (1995)). In the illustrative example, Applicant describes monoclonal antibodies that bind to the murine and rat RET antigen. See pages 17-18 of the specification. However, one skilled in the art would expect to be able to practice the claimed invention using other reagents that bind to the RET antigen. As such, Applicant requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-7 and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, objected to is the phrase "RET antigen" and the spelling of fluorochrome. Applicant traverses.

The metes and bounds of the subject matter is evaluated by "whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." MPEP 2100-160, § 2171. The specification on page 7 indicates that the sequence of RET is known from several organisms (Hesketh, ed., The Oncogene Facts Book, Academic Press Limited, pp.241-245 (1995)), indicating that the "RET antigen" is known to one skilled in the art. Moreover, Applicant points out that the claimed subject matter is not drawn to a RET antigen as RET is known and described in the art. Therefore, the Applicant requests that the rejection be withdrawn.

Applicant has corrected the spelling of fluorochrome in Claim 7. Thus, Applicant requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102 (a)

Claims 1-14 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Lo et al Neuron, 15: 527-539 (1995) (Lo). Upon review of this application, Applicant

believes Liching Lo is an inventor. As such, the claimed subject matter has not been invented by others more than a year prior to filing the application as required to support a rejection under Section 102(a). Therefore, it is requested that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102 (b)

Claims 1-3 and 8-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated. Specifically, Claims 1-3 are anticipated by Martucciello et al., J. Ped. Surg., 30(3): 433-436 (1995) (Martucciello); and Claims 8-11 are anticipated by Stemple and Anderson, Dev. Biol., 159: 12-23 (1993) (Stemple 1993), Stemple and Anderson, Cell, 71: 973-985 (1992) (Stemple 1992), Vescovi et al., Soc. Neurosci. Abstr., 19(103): 871, Abstract # 360.12 (1993) (Vescovi) and Reynolds et al., Soc. Neurosci. Abstr., 18:1107, Abstract 467.3, (1992) (Reynolds). Applicant respectively traverses.

Requirements for anticipation

In order for a reference to anticipate the claimed invention under 102(b), it must disclose each and every element of the claim within its four corners. In re Bonds, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Moreover, "[t]o be prior art under Section 102(b), the reference must put the anticipating subject matter at issue into the possession of the public through an enabling disclosure." Chester v. Miller, 15 USPQ2d 1333, 1336 (Fed. Cir. 1990).

Claims 1-3

The disclosure of Martucciello summarized

Martucciello discloses that the Ret R5 monoclonal antibody binds to the extracellular domain of the Ret protein (see e.g. p. 434, column 1). The antibodies were used to identify the presence or absence of ganglion cells in the colon. Ganglion cells are defined as nerve cells having their body outside the central nervous system (CNS).

As depicted in Figure 1 of the specification, nerve cells (neurons) differ from neuronal progenitor cells.

Martucciello does not disclose the subject matter of Claims 1-3

Claims 1-3 have been amended to recite that the RET antigen is bound to a cell selected from the group consisting of a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell and a committed neuronal progenitor (NP) cell. As indicated in Figure 1 of the specification, each of these cells can be differentiated from one another, as well as from neurons.

Thus, Martucciello does not disclose each and every element, since Martucciello does not disclose the cells which the RET antigen is bound to. Specifically, Martucciello does not suggest the cell types required by the claims as amended, a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell or a committed neuronal progenitor (NP) cell. As Martucciello does not disclose each and every element of the claims within its four corners, Martucciello does not anticipate the claimed subject matter. Applicant, therefore, respectfully requests that the rejection be withdrawn.

Claim 8

Stemple 1993

Stemple 1993 is a review which addresses advances and future directions in neural crest development. Some fractionation of subpopulations of cells by antigen expression is generally discussed, i.e., antibodies binding to ganglia and glial epitopes are discussed (page 17). The issue of whether neural crest cells are multipotent or precommitted is discussed (page 17). A substantially pure population of cells as claimed in amended Claim 8 is not disclosed.

Stemple 1992

Stemple 1992 discloses fluorescence activated cell sorting fractionation of neural stem cells using an antibody to low affinity nerve growth factor receptor. Figure 8 shows the subpopulations derived from the neural crest stem cells using the antibody.

Specifically, peripheral neurons, Schwann cells and "O cells" are identified. Multipotent neuronal progenitor (proNP) cells, nonneuronal progenitor (NNP) cells or committed neuronal progenitor (NP) cells are not disclosed.

Vescovi

Vescovi discloses CNS neural progenitor cell populations with neuronal or glial developmental potential that are EGF dependent. Cells derived from the neural crest are not disclosed.

Reynolds

Reynolds discloses CNS neural progenitor cell populations with neuronal or astrocyte developmental potential that are EGF-responsive. Cells derived from the neural crest are not disclosed.

Claim 8 is not anticipated by the publications

Claim 8 has been amended to name the types of neuronal progenitor cell populations which are substantially pure.

Stemple 1993 does not disclose substantially pure populations of multipotent neuronal progenitor (proNP) cells, nonneuronal progenitor (NNP) cells, or committed neuronal progenitor (NP) cells (see page 25 of the specification). Rather, Stemple 1993 raises the question of whether intermediate cell types are formed between multipotent cells and the ultimate derivative cell types, but provides no answer (page 20). Moreover, while Stemple 1993 indicates that neural crest cells are multipotent, Stemple 1993 does not disclose a substantially pure population of such.

In addition to disclosing each and every element in order to anticipate, Stemple 1993 must enable the claimed invention with a reasonable expectation of success. While Stemple 1993 makes a general suggestion that cells can be separated by their antigens such as HNK-1+ and HNK-1- cells, there is no indication that these markers would lead to multipotent cells, NP or NNP cells. For example, HNK apparently is a marker for melanogenic and/or catecholaminergic capacity (see page 17). Moreover, HNK is known to be a marker to a carbohydrate antigen on avian embryos. Stemple 1993 makes

no suggestion or slight indication that such a marker could be used to arrive at the claimed subject matter. Thus, even if Stemple 1993 disclosed the subject matter of Claim 8, which Applicant contends it does not, Stemple 1993 does not enable the subject matter of Claim 8, and therefore, does not anticipate.

In contrast, Applicants point out that they did not just find a marker which could generally be used to separate cells into groups. Rather, for the first time, a marker which identifies the cell types of Claim 8 has been identified, and for the first time, the claimed cell populations have been substantially purified.

Stemple 1992 does not disclose each and every element of Claim 8. The monoclonal antibody used in Stemple 1992 was directed against the low affinity nerve growth factor receptor (LNGFR) (see page 974 of Stemple 1992). This antibody was used to identify the lineage of cells set forth in Figure 8 of Stemple 1992, i.e., neural crest stem cells, peripheral neurons, Schwann cells and "O cells" (other uncharacterized cells). Stemple does not disclose the cell types of Claim 8. In particular, Stemple does not disclose the cells which proceed the neurons and Schwann cells, the neuronal progenitor cells. As Stemple 1992 does not disclose the claimed subject matter, Stemple 1992 does not anticipate.

Vescovi discloses cells isolated from mouse and human CNS. In contrast, the claimed invention is drawn to neural crest derived cells which form the neurons and glial cells of the peripheral nervous system (PNS). The neurons and glial cells from the PNS substantially differ in embryonic origin and development as well as function from those of the CNS. Moreover, Vescovi discloses cells that are EGF dependent (or responsive) not RET dependent, indicating that one could not arrive at the claimed invention from Vescovi. Therefore, Vescovi does not anticipate.

Reynolds discloses neural progenitor cell populations with neuronal or astrocyte developmental potential isolated from the CNS. Again, the claimed invention is drawn to neural crest derived cells which substantially differ in embryonic origin and development as well as function from those of the CNS. Furthermore, Reynolds uses

EGF-responsive stem cells, indicating that the present invention is not enabled by Reynolds. Therefore, Reynolds does not anticipate.

In conclusion, these papers, Stemple 1993, Stemple 1992, Vescovi and Reynolds do not disclose each and every element of the Claim 8 within their four corners nor do they enable the subject matter of Claim 8. Applicant, therefore, respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102 (e)

Claims 1-3 and 8-11 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,411,883 to Boss et al. (Boss). Applicant traverses.

In order for the present invention to be anticipated by a published patent, the reference must disclose each and every element of the claimed invention.

Boss discloses the isolation of CNS neuron progenitor cells isolated from an area of the brain that is enriched in potential dopaminergic cells. In contrast, the Applicant's invention is drawn to neural crest derived cells which substantially differ in embryonic origin and development as well as function from those of the CNS. Moreover, the skilled artisan would not arrive at Applicant's invention from Boss because Boss starts with material from the CNS and isolated the cells by using a culture medium system. Accordingly, Boss does not anticipate the present claims, and as such Applicant requests the rejection to be withdrawn.

Rejections under 35 U.S.C. § 103(a)--Claims 1-3

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hesketh, ed., The Oncogene Facts Book, Academic Press Ltd.: San Diego, pp. 241-245 (1995) (Hesketh) in view of Martucciello, Campbell, Monoclonal Antibody Technology, Elsevier, Amsterdam, pp. 1-4, 29 (1984) (Campbell), Harlow et al. Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring. pp.72-77 (1988) (Harlow) and Maurer et al., Meth. Enzymology, 70: 49-70 (1980) (Maurer). According

to the Office Action, it would have been obvious to generate monoclonal antibodies against RET in order to generate a potentially unlimited source of homogeneous reagent for affinity purification, functional studies or clinical studies of the RET protein. Applicant traverses.

Review of the publications

Hesketh

Hesketh discloses the cellular location, tissue distribution and amino acid sequence of RET.

Martucciello

Martucciello discloses RET antibodies used for immunohistochemical localization of the protein.

Campbell

Campbell discloses affinity purification uses of monoclonal antibodies.

Harlow

Harlow teaches to elicit antibodies to peptides (& synthetic peptides) and/or fusion proteins for uses such as functional and clinical studies.

Maurer

Maurer discloses the method to elicit an immune response by using a correct "carrier" and conjugation procedure.

The requirements to determine obviousness

To determine that an invention is obvious, one must determine that (1) the references cited disclose each of the claimed elements, (2) the references cited provide a suggestion within the references to combine the elements, and (3), the references provide a reasonable expectation of success in practicing the claimed invention. In this case, a determination of obviousness cannot be made.

The references do not disclose all of the claimed elements

Claims 1 and 2 have been amended to indicate that the antibodies are bound to a particular cell type. The element that the antibody is bound to a proNP, NNP or NP is not suggested or disclosed in Hesketh, Martucciello, Campbell, Harlow, or Maurer.

The references do not suggest that the claimed elements be combined

Even if Hesketh, Martucciello, Campbell, Harlow or Maurer disclosed all the claimed elements, which they do not, there is no suggestion to combine the elements to arrive at the claimed invention.

The references do not provide a reasonable expectation of success

Since the references do not disclose or suggest the claimed elements, nor that such elements can be combined, they do not provide a reasonable expectation that the claimed invention could be practiced with success. Applicant submits that the claims are not obvious over Hesketh in view of Martucciello, Campbell, Harlow and Maurer. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. § 103--Claims 4-14

Claims 4-14 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Lo et al., Perspectives Dev. Neurobiol., 2:191-201 (1994) (Lo 1994), Stemple 1993, Stemple 1992 and Martucciello. The Office Action states that according to these references, it would have been obvious to one of ordinary skill in the art at the time of instant invention to use antibodies for the immunological fractionation of RET+ cells by conventional methods such as fluorescence activated cell sorting. In addition, the Office Action states, "one of ordinary skill in the art would have had an extremely reasonable expectation that the conventional methods taught by the references would function as

desired and produce a desired cell population with the desired marker". Applicant traverses.

A review of the publications

Lo 1994

Lo discloses MASH-1, and mentions a possibility of interaction between MASH-1 and c-ret. Lo discloses that "[i]rrespective of their function and regulatory interrelationship, (undisclosed), MASH-1 and c-ret provide valuable markers for very early stages in neural crest cell lineage diversification" (page 199). What c-ret is determinative of is not disclosed. A schematic illustrating the role of MASH-1 in neural crest development is provided in Figure 6. This schematic is "postulated", each of the populations of cells were not purified (see legend of Figure 6). The legend of Figure 6 states:

This scheme is purely speculative, for example, it is not clear whether progenitors committed to an autonomic fate can generate both neurons and glia or, as the diagram implies, only neurons.

Stemple 1993

Stemple 1993 is a review which discloses there is developmental heterogeneity in the neural crest population, and is further discussed above.

Stemple 1992

Stemple 1992 discloses fluorescence activated cell sorting for fractionation of neural stem cells of varying developmental potentials by using an antibody to low affinity nerve growth factor receptor (LNGFR) and is further discussed above.

Martucciello

Martucciello discloses the R5 Ret monoclonal antibody which binds to the extracellular domain of the RET protein in ganglia.

The requirements for obviousness

The requirements are as stated above. Moreover, the Applicant adds the following case law as pertinent below.

While any invention may be "obvious to try", the "obvious to try" criterion is not sufficient to support a rejection under 35 U.S.C. § 103. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). See also The Gillette Co. V. S.C. Johnson & Sons, Inc., 16 USPQ2d 1923 (CAFC 1990). Applicant would like to direct the Examiner to In re Vaeck, 20 USPQ2d 1438, 1442 (CAFC 1991) where the Federal Circuit stated:

a proper analysis under § 103, inter alia, consideration of two factors; (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would have also revealed that in so making and carrying out, those of ordinary skill would have a reasonable expectation of success...Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

Thus, for a combination of references to render a claimed invention obvious under 35 U.S.C. § 103, that combination must provide not only a suggestion of the present invention, but also a reasonable expectation of success in reaching that invention.

The invention

Claims 4-7 are drawn to a method, and Claims 8 and 12-14 are drawn to substantially pure cell populations. Applicant reviews that the claimed methods and cell populations are not based on the discovery of RET and whether or not it may be marker. Rather, the claimed invention is based on the identification, for the first time, of the lineage of neural crest stem cells, from an uncommitted neural crest stem cell, to a committed neuronal progenitor cell, or a nonneuronal progenitor cell.

Committed neuronal progenitor cells are cells whose fate cannot be diverted by exposure to environmental factors known to suppress neuronal differentiation by multipotent stem cells. The present invention shows challenges to such factors, i.e.,

GGF and fibronectin thus providing committed neuronal progenitor cells for the first time. While there may have been some indication that RET was a marker of some sort, the particular lineage or biological properties was not predicted or suggested. In particular, prior to the present invention, it remained a controversy as to whether multipotent stem cells directly generate postmitotic neurons as the immediate daughters of asymmetric cell divisions, or whether such stem cells first produce lineage-restricted neuronal progenitor cells that then undergo a limited number of symmetric divisions prior to mitotic arrest and neuronal differentiation. The skilled artisan could not have predicted that this ongoing controversy would be resolved by the use of RET, which was known in the art while the controversy existed and was ongoing, unresolved.

No reasonable expectation of success

As indicated above, each element must be disclosed and there must be a reasonable expectation of success in practicing the claimed invention to render it obvious over the prior art. Applicant submits that a substantially pure population of proNP, NNP or NP cells as claimed in Claim 8 are not disclosed. Moreover, there is no reasonable expectation of success that RET positive cells would result in an enrichment of neural progenitor cells. As indicated above, what may be obvious to try, is not obvious to succeed, and what is not reasonably expected to succeed, is not obvious under Section 103.

Specifically, Lo states that "it is not clear whether progenitors committed to an autonomic fate can generate both neurons and glia or, as the diagram implies, only neurons" (Figure 6 legend). As such, there is no reasonable expectation of success from Lo, since Lo explicitly states that "it is not clear" which model is expected to succeed, since there are at least two possibilities. Stemple 1993, Stemple 1992 and Martucciello do not clarify this issue to arrive at the claimed invention. Since these references do not provide an expectation of success, there cannot be a determination of obviousness over these references.

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In view of the above amendments and remarks and the accompanying Declaration, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 2, 4-8 and 12-15. Applicant believes the claims stand in condition for allowance. Applicant earnestly solicits such allowance.

Respectfully submitted,

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